REMARKS

Applicants have the following comments in support of this amendment.

Claim Amendments - Reference to the Disclosure

Independent Claims 1, 16, 22, 29, 46 and 47 have been amended to be more explicitly directed to a preferred embodiment of the present application, i.e. intracorporeal radiosensitizer pharmaceutical compositions and medicaments consisting of various formulations of certain halogenated xanthenes selected from a group consisting of:

- 4,5,6,7-Tetrabromoerythrosin,
- Monobromoerythrosin,
- Dibromoerythrosin,
- Tribromoerythrosin,
- Monochloroerythrosin,
- Dichloroerythrosin,
- Trichloroerythrosin,
- Monofluoroerythrosin,
- Difluoroerythrosin,
- Trifluoroerythrosin,
- 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein,
- 2',4,5,6,7,7'-Hexafluorofluorescein, and
- 4,5,6,7-Tetrafluorofluorescein.

Dependent Claims 3, 18, 23, 31 and 50 have been made independent and are directed to another preferred embodiment of the present application, i.e. intracorporeal radiosensitizer pharmaceutical compositions and medicaments consisting of various formulations of certain halogenated xanthenes selected from a group consisting of:

- disodium Diiodofluorescein,
- disodium Eosin B,
- disodium Eosin Y,
- disodium Erythrosin B,
- disodium Phloxine B, and
- disodium Rose Bengal.

These halogenated xanthenes were previously the subject of dependent Claims 3-5, 18, 19, 23, 24, 31-33 and 50 (some of which have been canceled in favor of their respective independent claims), and are enumerated in the specification of the present application at, for example, p. 10, lines 14-20, and in Table 1.

Further, independent Claims 3, 18, 23, 31 and 50 have been amended to recite that the claimed forms of Diiodofluorescein, Eosin B, Eosin Y, Erythrosin B, Phloxine B and Rose Bengal are the disodium salts, as shown in Table 1, which illustrates that groups R^1 and R^2 of this subset of the halogenated xanthenes (see Figure 1b for the structural designation of these groups) may be, for example, sodium (i.e., Na).[1]

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[1] These claims recite that each of the halogenated xanthenes are disodium salts. Previously, Applicants advised the Examiner that neither Serafini et al. (Journal of Nuclear Medicine, 1975) nor Fondren et al. (Environ Entomol) disclosed or suggested potassium or sodium salts of halogenated xanthenes. The Examiner thereafter withdrew the rejection over these references (though the specific reason(s) for such withdrawal was not given). As neither of

Accordingly, Applicants respectfully submit that the amendments have not added any new matter, and that the amendments to the claims are clearly supported by the original application as filed. Therefore, it is respectfully requested that these amendments be entered and considered at this time.

Novel Composition of Matter

Amended independent Claims 1, 16, 22, 29, 46 and 47 are directed to various pharmaceutical compositions that contain novel, highly-halogenated halogenated xanthenes (i.e., 4,5,6,7-Tetrabromoerythrosin, Monobromoerythrosin, Dibromoerythrosin, Tribromoerythrosin, Monochloroerythrosin, Dichloroerythrosin, Trichloroerythrosin, Monofluoroerythrosin, Difluoroerythrosin, Trifluoroerythrosin, 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein, 2',4,5,6,7,7'-Hexafluorofluorescein, and 4,5,6,7-Tetrafluorofluorescein), none of which are believed to have been described in the prior art.[2] Due to the relative complexity of synthesis of such compounds and other factors, such as stability considerations, Applicants believe they have invented new compounds which represent a novel extension to the halogenated xanthene family. For example, Rose Bengal (which formerly comprised the most halogen-rich member of the halogenated xanthene family) has been known for over 100 years. Nonetheless, knowledge of its properties and those of the other

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these references disclose or suggest disodium salts, these rejections should remain withdrawn.

[2] Some of these compounds are also the subject of independent claims in other applications of the assignee, such as application nos. 09/900,355 filed July 6, 2001 (US publication 2002-0161035) and 09/382,622 filed August 25, 1999 (which is a divisional of US 6,331,286 - which is already of record in this application). Terminal disclaimers have already been filed in the present application over the '622 application and US 6,331,286. While the claims of these other applications are directed to different subject matter than the present application, out of an abundance of caution Applicants are cited them herein in the enclosed IDS.

previously known halogenated xanthenes (such as phloxine B, erythrosin, and eosin) has not led those skilled in the art (prior to Applicants' conception) to conceive, suggest, synthesize or investigate these currently claimed highly-halogenated halogenated xanthenes. Nor has anyone else conceived of pharmaceutical compositions consisting of halogenated xanthenes for any radiosensitization prior to Applicants' work. Accordingly, Applicants respectfully submit that the claimed highly-halogenated halogenated xanthenes, and the various claimed pharmaceutical compositions containing such highly-halogenated halogenated xanthenes, of the claims of the present application are novel over the prior art.

Amendment of the Specification - Reference to the Disclosure

Applicants are amending the specification to clearly recite that the halogenated xanthenes of the present invention do not contain a radioisotope and are therefore not radioactive. Although the specification as filed clearly indicates that the halogenated xanthenes of the present invention do not contain a radioisotope and are therefore not radioactive, this amendment serves to clarify this aspect of the claimed invention in unambiguous language. Support for the proposed amendment may be found throughout the specification as filed, as described for example below.

The specification makes it clear that one of the primary objects of Applicants' invention is to maximize the effects of applied radiation in the treatment area while minimizing radiation exposure elsewhere in the body. To accomplish this object, the claimed pharmaceutical compositions and medicaments, and all components therein, are not radioactive. This is shown in the specification, for example, in the Field of the Invention that notes the purpose of the claimed invention as follows:

> "The present invention is directed to certain radiodense medicaments and methods for treatment of human or animal tissue using such medicaments in combination with radiation therapy, wherein these radiodense medicaments serve as radiosensitizers in high energy phototherapy." (p. 1, lines 11-13)

As is common knowledge in the art, radiosensitizers function by working in conjunction with separately applied radiation, as evidenced by the following passage from the Description of the Related Art in the specification:

> "Diseased tissue or tumors ... are often treated using high energy, highly penetrating *ionizing radiation* ... in a process known as *radiation therapy.*
>
> "Conventional radiation therapy ... generally works by attacking rapidly growing cells with ionizing radiation.... Unfortunately, using rapid growth as the sole targeting criterion does not limit the effects of such treatment to diseased tissue, and as a result, *heathy tissue is often destroyed or damaged.*
>
> "As a result, some improvements have been made in the *methods for delivery of the radiation to the disease site* so as to limit the effects of such radiation to the general area of the diseased tissue. However, since healthy tissue and diseased tissue typically have a similar biological response to ionizing radiation, a need exists to *improve the potency* of (or biological response to) the *delivered radiation within the vicinity of the diseased tissue ... so as to not affect the surrounding healthy tissue.*
>
> "Accordingly, some investigators have focused their efforts on developing *agents that become activated by, or increase the therapeutic potential of, such ionizing radiation.* Such agents are known as *radiosensitizers*, and when *used in combination with ionizing radiation* constitute a therapeutic modality known as high energy phototherapy. Since *radiosensitizers function by absorbing* or otherwise interacting with penetrating, ionizing radiation and locally transforming this radiation into a more biologically active form, it is desirable that such radiosensitizer agents exhibit high intrinsic radiodensity and a capacity for preferential concentration in diseased tissue (thus allowing maximal, selective delivery of the therapeutic effects of such radiation to such diseased tissue containing such agent)." (p. 2, line 7 - p. 3, line 7, emphasis added)

Thus, radiosensitizers improve upon radiation therapy (i.e., treatment of disease by application of radiation) by functioning in combination with applied ionizing radiation to increase the therapeutic potential of such radiation. Specifically, as described *supra*, radiosensitizers serve to *absorb applied*

ionizing radiation in a manner that improves the local potency of the radiation in diseased tissue while not affecting surrounding healthy tissue.

A key feature of such radiosensitizers is that they should be non-toxic in the absence of applied radiation, as described in the following passage:

> "However, a high light cytotoxicity is not enough to make an agent an acceptable agent. The agent must also have a *negligible effect when energy is not applied* (i.e., have a *low toxicity in the absence of radiation*, or "dark cytotoxicity"). (p. 4, lines 4-6, emphasis added)

Thus, desirable radiosensitizers are not toxic in the absence of separately applied radiation. Since ionizing radiation is inherently toxic (i.e., by definition ionizing radiation is capable of breaking molecular bonds, thereby resulting in toxic biological effects), this passage makes it clear that radiosensitizers as a class are not toxic and hence not radioactive. Moreover, Applicants make it clear that the claimed radiosensitizers are similarly non-toxic in the following passage from the specification:

> "Selected chemical and physical properties ... of representative halogenated xanthenes are summarized in attached Table 1.... In general, the halogenated xanthenes are characterized by a large radiation absorbance cross-section, *low dark cytotoxicity (toxicity to cells or tissues in the absence of radiation*), high light cytotoxicity (toxicity to cells or tissues upon irradiation), relatively low cost, an ability to clear rapidly from the body, and chemical and radiosensitizer properties that are substantially unaffected by the local chemical environment or the attachment of functional derivatives at positions R^1 and R^2." (p. 9, line 15 - p. 10, line 5, emphasis added)

As defined *supra* with regard to the general class of radiosensitizers, the relevant halogenated xanthenes are not toxic to cells or tissues in the absence of applied ionizing radiation, and must be non-radioactive. If they are non-radioactive, such claimed halogenated xanthenes must also not contain any radioisotopes.

Second, since radiosensitizers are expected to function by absorbing radiation rather than emitting it, they are by definition non-radioactive. To one skilled in the art, the present application clearly teaches away from using a radiosensitizer that contains a radioisotope, since such a hypothetical composition would not be suitable for absorbing radiation nor would it be non-toxic in the absence of applied radiation. Instead, it would emit radiation and be inherently toxic, both of which are antithetical to the meaning of a radiosensitizer. Accordingly, one skilled in the art would clearly understand from Applicants' specification that the present invention excludes use of halogenated xanthenes that are radioactive (and hence contain a radioisotope) since such halogenated xanthenes would be counter to definition of a radiosensitizer.

Third, the molecular weights (mw) listed in Table 1 for the representative halogenated xanthenes exclude all radioisotopes, since such radioactive analogs would have different molecular weights than those listed. For example, incorporation of a single atom of the radioactive ^{131}I isotope into rose bengal (for instance, by substitution of a single ^{131}I atom for one of the four atoms of naturally occurring, stable iodine isotopes that are present in the non-radioactive form of the molecule) would increase the molecular weight of the molecule from 1018 g to 1022 g. Accordingly, it would be clear to one skilled in the art, upon inspection of the listed molecular weights in Table 1, that Applicants' specification excludes incorporation of a single radioisotope in any of the listed examples of the halogenated xanthenes.

Fourth, the example molecular structures shown in Figures 1a and 1b do not indicate the presence of a radioisotope in the structure of the halogenated xanthenes. Since radioisotopes are typically not naturally occurring (particularly in the case of halogens, which have very short half-lives and must thus be manufactured in a reactor), it is normal convention in the art to indicate these

in a chemical structure. The absence of such designation in the structures shown in Figures 1a and 1b clearly conveys to the skilled artisan that Applicants' specification excludes incorporation of radioisotopes in the claimed halogenated xanthenes.

Fifth, when the chemical formula or name of a radiolabeled molecule is written (see, for example, Serafini, who describes "Iodine-123-rose bengal" and contrasts this to the non-radioactive form, i.e., "rose bengal"), it is convention to clearly designate the existence of all radioisotope in such formula or name.[3] The absence of such designation in the chemical names used throughout Applicants' specification further conveys to one skilled in the art that the present application excludes incorporation of radioisotopes in the claimed halogenated xanthenes.

For at least the above-stated reasons, Applicants respectfully submit that the specification, as filed, of the present application clearly supports the amendment to the specification herein, which excludes incorporation of radioisotopes in the halogenated xanthenes of the present invention. Such support is based at least on the molecular weights for the representative halogenated xanthenes listed in Table 1, on the example molecular structures shown in Figures 1a and 1b, and on the low dark toxicity of such halogenated xanthenes. Applicants therefore submit that such amendment does not add new matter to the application and respectfully request that the amendment be entered.

Applicants will now address each of the Examiner's rejections and comments in the order in which they appear in the Office Action.

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[3] Serafini et al. - J. Nucl. Med. 16 (1975) 629-633, of record.

Claim Rejections – 35 USC §112

35 USC §112, second paragraph

In the Office Action, the Examiner rejects Claims 16-21 under 35 USC §112, second paragraph, as being indefinite and under 35 USC §101 as reciting a use without reciting any steps. This rejection is respectfully traversed.

Although Applicants traverse this rejection, in order to advance the prosecution of this application, independent Claims 16 and 18 has been amended to recite wherein said halogenated xanthene is added to said pharmaceutical delivery vehicle to form said medicament and to correct informalities in claim language. It is respectfully submitted that these amendments overcome the Examiner's objections, and it is respectfully requested that these rejections be withdrawn.

35 USC §112, first paragraph

The Examiner also rejects Claims 1-5, 11-14, 16-33, 36-40 and 46-50 under 35 USC §112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

Although Applicants traverse this rejection, in order to advance the prosecution of this application, independent Claims 1, 16, 22, 29, 46 and 47 no longer include the language "sodium or potassium salt." Independent Claims 3, 18, 23, 31 and 50 have been amended to recite the dibasic salt forms of certain of the halogenated xanthenes. This is shown in the present application wherein Diiodofluorescein, Eosin B, Eosin Y, Erythrosin B, Phloxine B and Rose Bengal are the disodium salts, as shown in Table 1, which illustrates that groups R^1 and R^2 of this subset of the halogenated

xanthenes (see Figure 1b for the structural designation of these groups) may be, for example, sodium (i.e., Na). See discussion *supra*.

With regard to the limitation regarding the halogenated xanthene not including a radioisotope, the support for the feature is discussed in depth *supra*.

Accordingly, it is respectfully requested that the rejection of these claims under §112, first paragraph, be withdrawn.

Double Patenting

Claims 22-28 over copending Application No. 10/331,854

The Examiner also provisionally rejects Claims 22-28 under the judicially created doctrine of obvious-type double patenting over claims 41-45 of Applicants' copending Application No. 10/331,854. This rejection is also respectfully traversed.

Although Applicants traverse this rejection, in order to advance the prosecution of this application, a terminal disclaimer and fee are being filed herewith. As this disclaimer overcomes the Examiner's rejections, it is respectfully requested that this rejection be withdrawn.

Claims 22-28 over U.S. Patent No. 6,331,286

The Examiner also provisionally rejects Claims 22-28 under the judicially created doctrine of obvious-type double patenting over claims 1-2, 4-15, 17, 18, 20, 22-26, 28, 30 and 32 of U.S. Patent No. 6,331,286. This rejection is also respectfully traversed.

Although Applicants traverse this rejection, in order to advance the prosecution of this application, a terminal disclaimer has already been filed in this application over the '286 patent on

March 22, 2004. In light of this prior disclaimer, it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §102

Johansson

The Examiner further rejects Claims 1, 3, 5, 16, 18, 29, 31, 33, 36-38, 46, 47 and 50 under 35 USC §102(b) as being anticipated by Johansson (Svensk Farmaceutisk Tidskrift, 1973). This rejection is also respectfully traversed.

First, Johansson does not teach or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29, 46 and 47. Since Johansson fails to teach or suggest the existence of, or any use for, these halogenated xanthenes (such as for example 4,5,6,7-Tetrabromoerythrosin), Johansson cannot anticipate nor render obvious these independent claims or the claims dependent thereon. Hence, the rejection of these claims should be withdrawn.

Second, Johansson does not disclose or suggest the disodium salts of the halogenated xanthenes as recited in independent Claims 3, 18, 23, 31 and 50. Instead, Johansson describes a mono-sodium form of Rose Bengal in the article entitled, "Analysis and purification of Rose Bengal Sodium...." That this is a mono-sodium form of the molecule is clear from the abstract, which states:

> "Rose Bengal Na (I) here refers only to 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein Na."

Since the acid dissociation constants (pKa) of rose bengal are approximately 3.7 and 4.8, pertaining to the following equilibria:

$$RB \text{ (free acid)} \rightleftharpoons RB^- + H^+ \quad pKa_1 = 3.7$$

$$RB^- \rightleftharpoons RB^{2-} + H^+ \quad pKa_2 = 4.8$$

the mono-sodium (i.e., monobasic) form of rose bengal (i.e., RB^-) referred to by Johansson would yield an acidic composition whereas the disodium (i.e., dibasic) form of rose bengal (i.e., RB^{2-}) of Claims 3, 18, 23, 31 and 50 yields a neutral composition. Applicants have found through detailed experimentation that such neutral compositions exhibit targeting of diseased tissue as described in the specification of the present application, whereas acidic compositions appear not to provide such targeting. Accordingly, the form of rose bengal described in Johansson differs from that claimed in Claims 3, 18, 23, 31 and 50 both in chemical composition and functional activity. Hence, Johansson does not disclose or suggest the claimed invention, and the rejection of these claims should be withdrawn.

For at least the above-stated reasons, Johansson fails to disclose or suggest the pharmaceutical compositions, medicaments or uses of the independent claims of the present application. Accordingly, the claims of the present application are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

Crounse, et al.

The Examiner also rejects Claims 1, 3, 5, 16, 18, 29, 31, 33, 36-38, 46, 47 and 50 under 35 USC §102(b) as being anticipated by Crounse et al. (US 4,647,578). This rejection is also respectfully traversed.

First, Crounse does not disclose or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29, 46 and 47. Since Crounse fails to teach or suggest the existence of, or any use for, these halogenated xanthenes (such as 4,5,6,7-Tetrabromoerythrosin), Crounse cannot anticipate nor render obvious these independent claims or the claims dependent thereon. Hence, the rejection of these claims should be withdrawn.

Second, Crounse does not disclose or suggest the claimed pharmaceutical compositions, medicaments, and uses, nor does the reference in any way disclose or suggest the unexpected benefits achieved by the claimed compositions, medicaments and uses of the present application. In fact, Crounse is not at all relevant to the present invention, and one skilled in the art would not consider this reference in designing a pharmaceutical composition for treatment of diseases of human and animal tissue. Instead, Crounse describes *pesticidal uses* of *aqueous suspensions* of certain *water insoluble forms* of the halogenated xanthenes. Such uses and compositions do not include a pharmaceutical vehicle nor are they suitable for therapeutic treatment, as recited in the independent claims of the present application.

For example, the abstract in Crounse makes it clear that this reference pertains to certain uses of water insoluble free acids as insecticides:

> "*Water insoluble*, photodynamic *insecticidal compositions* comprising the *free acids* of erythrosin B, phloxin B, rose bengal, octabromofluorescein or fluorescein or the aluminum lakes thereof, optionally including a dispersant, aqueous dispersions of the same and a method of combatting adult insects and insect larvae by use of the same." (Abstract, emphasis added)

Such insecticidal compositions are not relevant to the therapeutic compositions of the present invention, since whereas pesticides are intended to kill organisms, therapeutic compositions are intended to help, cure or save the lives of organisms. Accordingly, Crouse teaches away from the curative subject matter of the present invention.

Third, Crounse does not disclose or suggest the water soluble, dibasic salts of the halogenated xanthenes (i.e., disodium erythrosin B, disodium phloxin B and disodium rose bengal) of independent Claims 3, 18, 31 and 50 of the present application. Instead, Crounse is directed to free acid forms having completely different chemical properties. For example, whereas the claimed halogenated xanthenes are highly water soluble dibasic salts, the free acids in Crounse are water

insoluble. Such water insoluble forms are not compatible with the compositions, medicaments and uses in independent Claims 3, 18, 31 and 50 of the present application, nor do the water insoluble forms in Crounse exhibit the same therapeutic activity (due to similar reasons as described *supra* with regard to Johansson). For instance, the partitioning properties of the water insoluble free acids, such as discussed in the present application on pages 11 and 12, are completely different from those of the water soluble molecules of the claimed invention. Accordingly, the free acid forms in Crounse do not afford the necessary activity of the dibasic salts of the claimed invention.

Fourth, to the extent that Crounse mentions water soluble forms of the halogenated xanthenes, such discussion is limited to statements regarding the alleged superiority of the insoluble forms of Crounse for insecticidal use, as shown in the following passages from Crounse:

> "... we have found that the aqueous suspensions of certain water insoluble xanthene dyes or their aluminum lakes ... have photodynamic insecticidal activity and, in fact, quite surprisingly they have *greater insecticidal activity than aqueous solutions of the corresponding water soluble sodium salts*." (col. 3, lines 13-19, emphasis added)

> "As stated above, certain water soluble sodium or potassium salts of xanthene dyes, such as erythrosin B, phloxin B and rose bengal, have long been known to have *photodynamic insecticidal activity*." (col. 4, lines 56-59, emphasis added)

Thus, contrary to the Examiner's statement on p. 10 of the Office Action, Crounse is directed to water insoluble versions of halogenated xanthenes and only discloses that the halogenated xanthenes can be used as insecticides. The safety issues referenced by the Examiner pertain to potential toxicity to humans when used as insecticides. Further, as shown above, Crounse teaches away from water soluble molecules and asserts that the water insoluble versions of Crounse are highly superior for insecticides (no mention being made of pharmaceutical compositions for therapeutic treatment, as in the claimed invention).

Fifth, although Crounse mentions certain water soluble forms of the halogenated xanthenes, these are not the same forms that are the subject of the claimed invention. For example, with regard to "Experiment 1" (col. 6, line 55 - col. 7, line 65), Crounse provides comparative data for certain xanthene dye sodium salts and their corresponding free acids. While this description is ambiguous concerning the identity of these "xanthene dye sodium salts", the data in Table Ia and Ib (col. 7) in Crounse is not. These tables list data for the following compounds:

"erythrosin B Na^+" vs "erythrosin B free acid"

"phloxin B Na^+"vs "phloxin B free acid"

"rose bengal Na^+"vs "rose bengal free acid"

Accordingly, this listing shows that the xanthene dye sodium salts identified by Crounse are the mono-basic salts, whereas the claimed invention of independent Claims 3, 18, 31 and 50 of the present application concerns the dibasic (i.e., disodium) salts of these halogenated xanthenes. Since Crounse does not disclose or suggest the claimed dibasic salts, the reference cannot anticipate nor render obvious these independent claims, and the rejection of these claims should be withdrawn.

Finally, in contrast to the insecticides of Crounse, Applicants have discovered, and describe in the present application, new therapeutic properties of the halogenated xanthenes. As evidenced by the discussion in Crounse (see col. 4, lines 61-63), prior to discovery by Applicants, the halogenated xanthenes were believed to be essentially non-toxic to humans. The present application, however, shows that upon application of ionizing radiation, the halogenated xanthenes exhibit unanticipated toxicity to diseased tissue. Accordingly, the claims of the present application recite a halogenated xanthene and ionizing radiation. Crounse fails to disclose or suggest the novel toxicity properties of the claimed invention while also failing to describe or suggest the claimed

pharmaceutical compositions, medicaments and uses of the present application. Instead, Crounse is not even relevant to such teachings.[4]

For at least the above-stated reasons, Crounse fails to disclose or suggest the pharmaceutical compositions, medicaments or uses of rejected independent Claims 1, 3, 16, 18, 29, 31, 46, 47 and 50 of the present application. Accordingly, these rejected independent claims and those claims dependent thereon are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

Dees et al.

The Examiner also rejects Claims 1-5, 11-14, 16-33, 36-40, and 46-50 under 35 USC §102(b) as being anticipated by Dees et al. (USP 6,331,286). This rejection is respectfully traversed as this rejection is improper and incorrect on a number of grounds.

First, this rejection cannot be based on 35 USC §102(b). The present application was filed on March 26, 2001 which is prior to the issuance of the '286 patent (which issued on December 18, 2001). Hence, as the issue date of the '286 patent is *after* the filing date of the present application, this cannot possibly be a §102(b) rejection which requires that the invention was patented or described in a printed publication more than one year *prior* to the filing date of the application to be patented.

Further, the present application is a continuation-in-part under 35 USC §120 of the application (USSN 09/216,787) for which the '286 patent is based. Therefore, for common subject

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[4] For example, Crounse does not describe or suggest a composition suitable for intracorporeal use as a pharmaceutical composition, which must be sterile and pyrogen free, such properties being known to those of skilled in the art to be required for use as pharmaceutical compositions.

matter, Applicants can claim priority to the filing date of the '286 patent. If the subject matter is not common, then by definition, it cannot be disclosed in the '286 patent. Hence, there can be no anticipation.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Heitz

The Examiner also rejects Claims 1-5, 11-13, 16-21, 29-33, 36-40, and 46-50 under 35 USC §102(b) as being anticipated by Heitz et al. (USP 4,846,789). This rejection is respectfully traversed.

First, Heitz does not disclose or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29, 46 and 47. Since Heitz fails to teach or suggest the existence of, or any use for, these halogenated xanthenes (such as 4, 5, 6, 7-Tetrabromoerythrosin), Heitz cannot anticipated nor render obvious the claimed invention. Hence, it is respectfully requested that the rejection of these claims be withdrawn.

Second, Heitz does not disclose or suggest the presently claimed therapeutic compositions, medicaments or uses. In fact, Heitz is not in any way relevant to the present invention, and one skilled in the art would not consider this reference in designing a pharmaceutical composition for treatment of diseases of human and animal tissue. Instead, Heitz is directed to pesticidal compositions and uses. This is clear from the following Summary of the Invention in Heitz:

> "The present invention utilizes the dyes described hereinafter and exposure to electromagnetic radiation to initiate one or more lethal photo-oxidative *reactions in certain internal parasites* of warm blooded animals. The parasites are endoparasitic helminths and/or pathogenic gastrointestinal protozoa having a life cycle which includes a life stage within the animals and a *life stage outside of the animals*. The parasites are *normally protected from exposure to natural electromagnetic radiation* having a wave length falling within the *visible spectrum* during at least most of the life stage within the animals, but

> they are *normally exposed to electromagnetic radiation* during at least a portion of the life stage *outside of the animals*
>
> "In practicing the method of the invention, *the internal parasites are caused to incorporate therein a photosensitizing amount of a dye.... Thereafter the parasites* having the dye incorporated therein *are exposed to electromagnetic radiation* of a wave length absorbed by the dye to thereby form cytotoxic oxygen and initiate at least one lethal oxidative reaction within the resulting photosensitized parasites. The parasites are preferably in the infective stage, thereby causing the life cycle to be broken. This markedly *reduces or prevents reinfection and the need for treating the animals with traditional anthelmintics.*" (col. 1, 33-62, emphasis added)

This passage makes it clear that the disclosure in Heitz pertains to pesticidal use (i.e., killing intestinal parasites). In fact, Heitz does not treat disease in the animal at all but rather prevents transmission of pathogens from one infected animal to another animal (i.e., the pathogenic organisms are killed outside of the infected animal before they can infect another animal). This is evidenced by the following passage from Heitz:

> "The aforementioned internal parasites ... should have a life cycle which includes a life stage within the host animal and a *life stage outside of the host animal.* The parasites are *protected from exposure to natural electromagnetic radiation having a wave length falling within the visible spectrum* during at least most, and preferably all or substantially all, of the life stage *within the host animal.* However, the parasites are normally *exposed to electromagnetic radiation*, which is usually *natural or artificial visible light*, during at least a portion of their life stage *outside of the host animal.*" (col. 2, line 50-61, emphasis added)

Hence, the pathogens are "treated" by exposure to electromagnetic radiation during a period when they are *outside of the host animal.* This exposure occurs in the feces of the animal host upon exposure to light energy outside of the body, killing pathogenic organisms in the feces and thereby preventing transmission to another host animal as explained in Heitz as follows:

> "As a general rule, the endoparasitic helminths usually reside in the gastrointestinal tract as adults and produce large numbers of eggs which are passed from the animal host in the feces... *The fecal pats are normally exposed to visible light*, and the *hatching eggs and larvae stages developing therefrom are likewise exposed to visible light....* In the presence of visible light,

> substantially all of the *larve are killed before they are able to reinfect* the animal host." (col. 5, line 48 - col. 6, line 20, emphasis added)

Accordingly, the disclosure in Heitz does not therapeutically affect the animal to which the photosensitive dye is fed, but rather serves to break the chain of transmission of pathogens from one infected animal to another once the pathogens are exposed to light outside of the host animal's body. Therefore, the disclosure in Heitz is not directed nor does it disclose or suggest an injectable radiosensitizer pharmaceutical composition (as required in Claims 1 and 3 in the present application); nor does it comprise use of a dye in the preparation of an intracorporeal radiosensitizer medicament (as required in Claims 16 and 18); nor does it comprise intracorporeal use of radiosensitizer medicament (as required in Claims 22 and 23); nor is it a radiosensitizer pharmaceutical composition (as required in Claims 29, 31, 47 and 50); nor is it even an intracorporeally-applicable radiosensitizer medicament (as required in Claim 46).

Third, Heitz does not disclose or suggest radiosensitization using applied ionizing radiation having an energy of greater than approximately 1 keV, as required in independent Claims 1, 3, 16, 18, 22, 23, 29, 31, 46, 47 and 50. Instead, as noted by the Examiner on pp. 10-11 of the Office Action, Heitz discloses use of light energy, including visible light, near infrared light, and near to far ultraviolet light. Such light has energy far below the 1 keV recited in the independent claims and underlies the fundamental reason why the disclosure in Heitz requires exposure of pathogens to light energy outside of the body (such light cannot penetrate into the body), whereas Applicants' claimed invention allows delivery of activating energy (i.e., highly penetrating ionizing radiation) to any location within the body, thereby allowing disease to be treated in situ. In fact, Heitz makes no disclosure or suggestion of any interaction of any sensitizing agent with ionizing radiation, and

therefore completely misses the topic of radiosensitization and is not in any way relevant to the present invention.

Fourth, the compositions in Heitz are not suitable for intracorporeal use, as recited in the claims of the present application, since they are not sterile nor pyrogen free, as one of ordinary skill in the art would understand to be required of any composition or medicament that is to be injected into or otherwise delivered into tissues of the body. Instead, Heitz describes certain animal feed additives which of course are generally not sterile nor pyrogen free, as evidenced by the following passage from Heitz:

> "The dye may be administered to the animal in the form of an additive to its daily feed ration, in capsules, compressed pellets, boluses, salt blocks and the like. In the case of poultry, the dye may be incorporated within a synthetic grit...." (col. 5, lines 25-29)

Consumption of such feed additives leads to absorption of a portion of the photosensitizing dye contained therein by parasites in the gastrointestinal tract of the animal as explained below in Heitz:

> "When the host animal is fed the dye described herein, the dye is admixed with the food to be digested and passes through the gastrointestinal tract. The dye is in contact with the exposed skin of the immature larvae stages and adult stages residing in the gastrointestinal tract, and it is also present in the food consumed by the adult nematodes. As a result, the nematodes in the immature larvae stages and/or adult stage appear to ingest, assimilate, absorb or otherwise incorporate the dye into their tissues." (col. 5, line 62 - col. 6, line 3)

Thus, the compositions in Heitz pass through the digestive system of the host without uptake into its tissues and do not, therefore, comprise compositions for intracorporeal delivery to, and for treatment of, diseased tissue in the animal.

Since the compositions in Heitz are not suitable for intracorporeal use as radiosensitizers, and since Heitz fails to teach or suggest the recited ionizing radiation energy levels, the fundamental properties, and mechanisms of Applicants' claimed radiosensitizer pharmaceutical compositions,

medicaments, and uses, Heitz cannot anticipate nor render obvious the claimed invention of the present application, nor is Heitz even relevant to the claimed invention. Hence, it is not a proper reference to reject the claims of the present application.

For at least the above-stated reasons, Heitz fails to disclose or suggest the pharmaceutical compositions, the medicaments or uses of the independent claims of the present application. Accordingly, the claims of the present application are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §103

Johansson or Crounse in view of Neckers

The Examiner also rejects Claims 2, 12, 14, 20, 30, 39 and 48 under 35 USC §103(a) as being unpatentable over Johansson or Crounse in view of Neckers. This rejection is also respectfully traversed.

Each of these is a dependent claim. As none of these cited references disclose or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29 and 47 for which these rejected claims depend, these claims are also patentable over the cited references, and this rejection should be withdrawn.

Additionally, in the Office Action, the Examiner admits that Johnsson and Crounse fail to teach applying ionizing radiation such as X-ray upon a halogenated xanthene. Hence, the Examiner's stated basis for this rejection appears to hinge on alleged teachings in Neckers of the interaction of the halogenated xanthenes with x-rays. However, in the Office Action of September 23, 2003, the Examiner acknowledged that Neckers fails to teach applying ionizing radiation at specifically greater than approximately 1 keV and less than approximately 1000 MeV (which the

Examiner admits Johnsson and Crounse also do not teach and continues to admit Neckers does not teach).

Nonetheless, in the present Office Action, the Examiner argues that Neckers has relevance because it teaches that "Rose Bengal, disodium salt is characterized ... by its capacity to be activated as an imaging agent, with X-ray..." (p. 12, third paragraph). The Examiner then alleges that "it would have been obvious to one of ordinary skill in the art at the time of the instant invention to apply X-radiation as taught by Neckers upon halogenated xanthenes as taught by Johansson and Crounse in order to effect activation of the compound because Neckers specifically taught that halogenated xanthenes can be activated by X-ray as imaging agents" (p. 12-13, forth paragraph).

Such allegations are in clear and direct contradiction to the Examiner's acknowledgment regarding what these references do not teach. Since Neckers does not teach any properties of the halogenated xanthenes with regard to ionizing radiation having an energy of greater than 1 keV, as previously acknowledged by the Examiner and required by the amended claims of the present application, this reference cannot be combined with the teachings of Johansson or Crounse to arrive at the claimed invention. Hence, these references fail to disclose or suggest the claimed invention and fail to provide a prima facie case of obviousness.

The Examiner, however, contends that the level of ionization is no more than mere routine experimentation to discover optimum values. Applicants respectfully disagree. As Applicants previously explained to overcome the Examiner's prior allegations regarding these aspects of the teachings in Neckers, Neckers' observation that Rose Bengal has properties as a photodynamic sensitizer has no relevance nor predictive value regarding possible interaction of the molecule with ionizing radiation having an energy of greater than 1 keV. As Applicants discussed in Amendment B in response to the September 23, 2003 Office Action, the highest energy noted in Neckers is 380

nm (Neckers p. 20, last line; a wavelength of 380 nm is equal to an energy of 0.003 keV). Physical, chemical or photosensitizer properties at energies less than or equal to 0.003 keV have no relevance or predictive value regarding potential radiosensitizer properties at energies of greater than 1 keV. Hence, the various properties of Rose Bengal, as noted in Neckers, are not relevant and cannot predict the composition of the claimed invention or the radiosensitizer properties discovered by Applicants with regard to the claimed invention.

Similarly, Neckers' observation that Rose Bengal exhibits fluorescence properties upon illumination with light at energies less than or equal to 0.003 keV has no relevance or predictive value regarding potential interaction of the molecule with radiation at energies of greater than 1 keV (i.e., as a contrast medium for such energies greater than 1 keV, including x-rays). The optical fluorescence properties of a given material arise from features that are completely unrelated to features that determine absorption of ionizing radiation having energies greater than 1 keV. Thus, knowledge that Rose Bengal exhibits fluorescence upon illumination with light has no relevance or predictive value regarding potential use with ionizing radiation at energies of greater than 1 keV. Hence, the fluorescence properties of Rose Bengal are not relevant and cannot predict the claimed invention or the radiosensitizer properties discovered by Applicants with regard to the claimed invention.

Accordingly, for at least the aforementioned reasons, Neckers has no relevance with respect to the properties of the halogenated xanthenes as delimited in the claims of the present application, nor to the compositions or medicaments of the claimed invention.

Moreover, as explained below, even if it was proper to combine these references (which Applicants do not admit),combining the teachings of Neckers with those of Johansson or Crounse fails to arrive at the present invention.

Johansson does not disclose the claimed compositions or uses.

As discussed in detail *supra*, Johansson does not disclose or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29, 46 and 47. Since Johansson fails to teach or suggest the existence of, or any use for, these halogenated xanthenes (such as 4,5,6,7-Tetrabromoerythrosin), Johansson cannot render obvious the claimed invention. Further, Johansson does not disclose or suggest the disodium salts of the halogenated xanthene as recited in the independent Claims 3, 18, 23, 31 and 50. Instead, Johansson describes a mono-sodium form of rose bengal. Hence, even if this reference was combined with Neckers, the combination would still fail to disclose or suggest the claimed invention.

Further, there is absolutely no discussion in Johansson on the issue of radiosensitization, neither teaching nor suggesting it in any capacity, nor suggesting any interaction of ionizing radiation having an energy of greater than approximately 1 keV with any halogenated xanthene or composition containing any halogenated xanthene. Accordingly, the teachings in Johansson are not relevant to the patentability of the claimed radiosensitizer compositions, medicaments and uses, nor to the claimed details concerning their use (such as specific activation energies or concentrations). Adding the teachings in Neckers to those in Johansson fails to arrive at the claimed invention since, rather than teaching halogenated pharmaceutical compositions or medicaments for radiosensitization with ionizing radiation having an energy of greater than approximately 1 keV, Neckers is directed to an entirely unrelated energy spectrum that is unsuitable for the present invention.

Crounse does not disclose the claimed compositions or uses.

As discussed in detail *supra*, Crounse does not teach nor suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29, 46 and 47. Since Crounse fails to teach or suggest

the existence of, or any use for, these halogenated xanthenes (such as 4,5,6,7-Tetrabromoerythrosin), Crounse cannot render obvious the claimed invention. Further, Crounse does not disclose or suggest the disodium salts of the halogenated xanthene as recited in the independent Claims 3, 18, 23, 31 and 50. Instead, Crounse describes certain free acid and mono-sodium forms of rose bengal and several other halogenated xanthenes. Hence, even if this reference was combined with Neckers, the combination would still fail to disclose or suggest the claimed invention.

Additionally, Crounse concerns certain pesticidal compositions, such compositions being in diametric opposition to the intracorporeal therapeutic compositions of the claimed invention. Finally, there is absolutely no discussion in Crounse on the issue of radiosensitization, neither teaching nor suggesting it in any capacity, nor suggesting any interaction of ionizing radiation having an energy of greater than approximately 1 keV with any halogenated xanthene or composition containing any halogenated xanthene. Accordingly, the teachings in Crounse are not relevant to the patentability of the claimed radiosensitizer compositions, medicaments and uses, nor to the claimed details concerning their use (such as specific activation energies or concentrations). Adding the teachings in Neckers to those in Crounse fails to arrive at the claimed invention since, rather than teaching halogenated pharmaceutical compositions or medicaments for radiosensitization with ionizing radiation having an energy of greater than approximately 1 keV, Neckers is directed to an entirely unrelated energy spectrum that is unsuitable for practicing the present invention.

For at least the above-stated reasons, Applicants respectfully submit that even if combined, the cited references fail to disclose or suggest the claimed invention. Further, the combination of the references to arrive at the claimed invention is improper. Therefore, it is respectfully requested that this rejection be withdrawn.

Johansson or Crounse in view of Neckers and Khaw

The Examiner also rejects Claims 11, 13, 17, 21, 39, 40 and 49 under 35 USC §103(a) as being unpatentable over Johansson or Crounse in view of Neckers and in further view of Khaw. This rejection is also respectfully traversed.

Each of these is a dependent claim. As none of these cited references disclose or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29 and 47 for which these rejected claims depend, these claims are also patentable over the cited references, and this rejection should be withdrawn.

Additionally, for the reasons discussed above, these claims are also patentable over Johansson, Crounse and Neckers.

Further, the Examiner's stated basis for this rejection appears to hinge on alleged teachings in Khaw concerning (a) liposomal targeting and (b) gamma imaging. While Applicants traverse this rejection as discussed above, in order to advance prosecution of the application, Applicants have amended the independent claims to exclude liposomes, rendering Khaw irrelevant on the issue of liposomal targeting. Concerning gamma imaging, Applicants vigorously dispute the relevance of Khaw to the claimed invention, since Khaw teaches use of *gamma-emission imaging for diagnostics* whereas the present invention concerns therapeutic *treatment with applied gamma radiation.*

As described in detail in Applicants' Amendment B in response to the Office Action of September 23, 2003, the teachings in Khaw are limited to use of gamma radiation in a diagnostic mode. To achieve this objective, Khaw teaches attachment of gamma-emitting radionuclides to diagnostic agents and subsequent imaging of their distribution in the body via detection of gamma emissions from such radiolabeled diagnostic agents.

In contrast, the independent claims of the present application are directed to non-radioactive pharmaceutical compositions which, by definition, do not contain gamma-emitting radionuclides. There is no similarity between the claimed invention and the teachings in Khaw with regard to use of gamma radiation, as the independent claims specifically recite that the claimed halogenated xanthenes do not contain a radioisotope (and hence contain no gamma-emitting radionuclides which are necessary in Khaw). Hence, the claimed compositions explicitly exclude the gamma-emitting substances taught in Khaw. Accordingly, Khaw has no relevance to the claimed invention.

Therefore, the cited references fail to disclose or suggest the claimed invention, and the claims are patentable thereover. Accordingly, it is respectfully requested that this rejection be withdrawn.

Heitz

The Examiner also rejects Claims 14 and 22-28 under 35 U.S.C. 103(a) as being unpatentable over Heitz. This rejection is also respectfully traversed.

Each of these is a dependent claim. As none of these cited references disclose or suggest the halogenated xanthenes recited in amended independent Claims 1, 16, 29 and 47 for which these rejected claims depend, these claims are also patentable over the cited references, and this rejection should be withdrawn.

Further, the Examiner's stated basis for this rejection appears to hinge on alleged obviousness of "the optimum workable ranges of the ionizing radiation levels" necessary to practice the claimed invention. (p. 17, first paragraph) However, since Heitz is concerned with photoactivation of certain halogenated xanthenes using light energy, not ionizing radiation, Applicants respectfully submit that Heitz has no relevance to such effective variable.

As noted *supra* with regard to the Examiner's §102(b) rejections over Heitz, Heitz discloses certain uses of light energy, including visible light, near infrared light, and near to far ultraviolet light. Such light has energy far below the 1 keV claimed in the present application, and underlies the fundamental reason why the disclosure in Heitz requires exposure of pathogens to light energy outside of the body (since such light cannot penetrate into the body) whereas Applicants' invention allows delivery of activating energy (i.e., highly penetrating ionizing radiation) to any location within the body, thereby allowing disease to be treated in situ. In fact, Heitz makes no disclosure or suggestion of any interaction of any sensitizing agent with ionizing radiation, and therefore completely misses the topic of radiosensitization and is not in any way relevant to the present invention.

The differences between the visible light, near infrared light, and near to far ultraviolet light of Heitz and the claimed ionizing radiation having energies greater than approximately 1 keV are certainly not trivial. The sources of such energy are completely different as are the mechanisms of interaction of such energy with matter. For example, one skilled in the art would not arrive at an x-ray machine upon any routine experimentation with a flashlight. Nor would one skilled in the art arrive at the claimed invention upon routine experimentation based on the teachings in Heitz.

Since the disclosure in Heitz fails to point in any way toward any application of ionizing radiation having energies greater than approximately 1 keV, the claims of the present application are patentable over Heitz, and it is respectfully requested that this rejection be withdrawn.

Information Disclosure Statement

Applicants filed information disclosure statements (IDSs) on March 10, 2005 and May 12, 2005 in the present application. Applicants are also filing an IDS herewith. It is respectfully requested that these IDSs be entered and considered prior to the issuance of any further action on this application.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this Amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: June 3, 2005

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